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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

TH

Office Action Summary	Application No.	Applicant(s)	
	09/322,289	SCHENK, DALE B.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *25 – 28, 33 – 34, 38 – 58, and 60 – 81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1–2, 4, 6 – 8, 10 - 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93–104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-2, 4, 6-8, 10-12, 17, 21-28, 31-37, 56-58, 60-90, and 93 - 104.

DETAILED ACTION

1. The remarks and amendments filed 30 October 2007 have been entered. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 28, 31 – 37, 56 - 58, 60 – 90, and 93 – 104 are pending.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 October 2007 has been entered.

Election/Restrictions

3. Claims 25 – 28, 33 – 34, 38 – 58, and 60 – 81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 19 December 2000.

4. Claims 1 – 2, 4, 6 – 8, 10 - 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 104 are under examination.

Withdrawn Rejections and Objections

5. The following rejections and objections set forth in the previous office action are withdrawn:

A. The provisional obviousness-type double-patenting rejection over copending 10/232030 is withdrawn. The claims in the '030 case are now drawn to a different invention.

B. The provisional obviousness-type double-patenting rejection over copending 10/890071 is withdrawn. The '071 application has been abandoned.

C. The provisional obviousness-type double-patenting rejection over copending 10/923469 is withdrawn. The claims in the '469 case do not explicitly require antibodies of IgG1 isotype as recited in the instant claims.

Maintained Rejections

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 82 – 90, 93 – 102, and 104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of antibodies which specifically bind Aβ protein to asymptomatic patients, does not reasonably provide enablement for prophylaxis of disease as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection stands for the reasons for the reasons previously made of record with respect to claims 82 - 90 and 93 - 102, and is expanded to new dependent claim 104 as well. Briefly, the specification sets forth working examples of reducing the prevalence of amyloid plaques in PDAPP transgenic mice. The scope of prophylaxis, as defined by applicant on p. 27 of the specification, includes elimination of the risk of disease. That is, the claim encompasses complete prevention of disease and total elimination of any possibility of ever coming down with the disease. The specification discloses that treatment with anti-Aβ antibodies decreases the number of plaques, it does not disclose prevention of all symptoms and does not disclose eliminating the risk of disease, as embraced by the definition of prophylaxis. The disclosure in the specification is not commensurate in scope with the breadth of the claims.

Applicant argues, on p. 11 of the remarks filed 30 October 2007, that the issue of whether the side effects of the treatment might be more proper for the FDA to consider than the Patent Office. While the decision in *In re Brana* cited by applicant does mention that such considerations are properly left to the FDA, this does not preclude the examiner considering whether the model provided (here, PDAPP mice) is appropriate for the claimed invention. As set forth on pp. 5 – 6 of the previous office action, the prior art indicated that decreasing the levels of Aβ in normal patients would quite likely be deleterious. The art was cited to support the examiner's assertion that the PDAPP mice, which over-express Aβ, are not a physiologically appropriate animal model for prophylaxis of disease in normal patients. While the results presented in the specification are supportive of the idea that reducing abnormally high levels of

Aβ can attenuate or delay some of the symptoms of Alzheimer's disease, this does not indicate that the levels of this protein should be decreased in asymptomatic subjects with normal protein levels. The art (Perez, Liu) was cited to indicate that this protein has a role in normal physiology, and to indicate that it should not be attenuated. As the specification fails to set forth any examples where decreasing Aβ levels below normal in wild-type animals is therapeutic, and the examiner cited sound scientific reasons as to why one skilled in the art would not expect success in treating any disease in such subjects, rather the artisan would expect to disrupt normal physiology.

Applicant "notes from the Examiner's comment in the penultimate sentence of the rejection that the Examiner may not be going so far as to allege that this [including elimination of risk of disease in the scope of the claim] alone would provide grounds for nonenablement." While certainly a few non-enabled embodiments can be included in a claim without the claim itself being non-enabled, as the scope and number of non-enabled embodiments increases, the claim itself is to be considered non-enabled. Note that in *Libel-Flarsheim Co. v. Medrad Inc.* (82 USPQ2d 1113) the Court of Appeals for the Federal Circuit recently ruled that claims which encompassed non-enabled embodiments, which the art had recognized to be non-enabled in the absence of a large degree of experimentation, were invalid.

For the reasons above and those previously made of record, the rejection for lack of enablement commensurate in scope with claim 82 is maintained. The remaining claims subject to this rejection depend from claim 82 but are not limited to enabled embodiments.

Double Patenting

7. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 104 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 19 of U.S. Patent No. 6,743,427. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the claims allow for administration of antibodies generically whereas in the issued claims the antibodies must bind a specific epitope of Aβ.

This rejection stands for the reasons of record. Applicant did not traverse the rejection but indicated a terminal disclaimer may be filed in the future. However no such disclaimer has been filed so the rejection stands for the reasons of record.

8. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 104 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 36 of U.S. Patent No. 6,761,888. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the instant case the claims allow for administration of antibodies generically whereas in the issued claims the antibodies must bind a specific epitope of Aβ. Note that the issued claims encompass therapeutic and prophylactic treatment, (see claim 1), administration of human IgG1 antibodies (claim 19), as well as humanized (claim 14), chimeric (claim 15), and monoclonal antibodies (claim 17).

This rejection stands for the reasons of record. Applicant did not traverse the rejection but indicated a terminal disclaimer may be filed in the future. However no such disclaimer has been filed so the rejection stands for the reasons of record.

9. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 104 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 38 of U.S. Patent No. 6,913,745. Although the conflicting claims are not identical, they are not patentably distinct from each other because they differ only in scope; the issued claims of the '745 patent are limited to administration of specific humanized antibodies whereas the instant claims are generic with respect to which antibodies are to be administered. Note that the issued claims encompass humanized (claims 12, 31), monoclonal (claims 16 and 35), and chimeric antibodies (claims 14 and 33).

This rejection stands for the reasons of record. Applicant did not traverse the rejection but indicated a terminal disclaimer may be filed in the future. However no such disclaimer has been filed so the rejection stands for the reasons of record.

10. Claims 1 – 2, 4, 6 – 8, 10 – 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 104 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 177, 196, and 198 of copending Application No. 10/828548 in view of Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 8 January 2001.

Applicant argues, on p. 11 of the remarks, that the claims in the '548 application the examiner had cited as the basis for this rejection have been canceled. While they have been canceled, new claims 177, 196, and 198 encompass administration of antibody 10D5 for

attenuating the symptoms of Alzheimer's disease. 10D5 is a monoclonal antibody of isotype IgG1. However 10/828548 does not explicitly claim administration of humanized antibodies.

Becker teaches administration of humanized antibodies (column 5 last paragraph) and specifically teaches that the methods of making them are known in the art (column 6 lines 41 – 52). Becker teaches that humanized antibodies are advantageous in that the degree of immunogenicity is decreased due to the lack of foreign epitopes (column 6 lines 31 – 40). However Becker does not explicitly teach IgG1 isotype antibodies for administration.

It would have been obvious to one of ordinary skill in the art to modify the method of the claims of the '548 patent to use humanized antibodies as taught by Becker, with a reasonable expectation of success. The motivation to do so would be to reduce the immune system reaction to the antibody.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 - 2, 4, 10 - 12, 22-24, 31-32, 36, 82-84, 88-90, 95-99, 101, and 103-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker (EP 0 613 007, published 18 February 1994, cited on IDS filed 8 January 2001) in view of Kuby (1997. Immunology, Third Edition, p. 123, cited in office action mailed 17 November 2006) and Adair et al. (WO 91/16928, cited in office action mailed 17 November 2006).

This rejection is maintained with respect to claims 1 - 2, 4, 10 - 12, 22-24, 31-32, 36 and newly extended to claims 82-84, 88-90, 95-99, 101, and 103-104. Claims 103 – 104 recite certain properties of the antibody. The examiner is unable to determine if the antibodies rendered obvious by Becker in view of Kuby and Adair have this property. However, inclusion of these claims in this rejection is proper as the claims recite no additional structural limitations beyond those of the parent claims. As the references render obvious administration of the antibodies of isotype IgG1 for the reasons of record and further explained below, claims 103-

104 are properly included even though the prior art references are silent as to a property which appears to be inherent; see MPEP § 2112.

Briefly, Becker teaches administration of antibodies raised against Aβ peptide for treatment of Alzheimer's disease. Becker specifically speaks to the advantages of using humanized antibodies; see columns 5 – 6. The reference also teaches diagnosis, i.e. administration to patients not yet known to have disease, as encompassed by claims 82-84, 88-90, 95-99, 101, and 104. The reasons why the limitations of the specific claims are met by the reference are set forth in the previous office action. Note claims 4, 10 - 12, 22-24, 31-32, 36 recite the same limitations as claims 84, 88-90, 95-99, and 101 respectively; they differ only in that the latter set of claims depend from claims 82-83 rather than 1-2. However Becker does not explicitly teach administration of antibodies of isotype IgG1 as recited in claims 1 and 82.

Kuby teaches the structure of human IgG isotypes and teaches that they vary in size and in the structure of the hinge region. Kuby further teaches that the subtle differences in amino acid sequences between the various IgG classes lead to differences in the hinge region, and that these subtle difference also lead to differences in biological activities of the various classes of IgG isotypes (p. 123 second column first complete paragraph). Finally Kuby teaches that the classes (or isotypes) are determined not by the antigen binding region but by the constant region, which remains constant for any given isotype independent of the antigen bound. However Kuby does not teach specific advantages of isotype IgG1.

Adair teaches that the binding affinity of humanized antibodies which bind to ICAM-1 varies with isotype. Adair teaches that IgG1 isotype binds more strongly than other isotypes, and this is due to the structure of the hinge and constant regions of IgG1, providing motivation to the artisan of ordinary skill to select IgG1 antibodies based on their strong ability to bind to antigens. See especially pp. 22 – 23. However Adair does not teach administration of antibodies that bind to Aβ protein as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to select antibodies of isotype IgG1, as suggested by Kuby and Adair, for use in the methods of Becker, with a reasonable expectation of success. The motivation to do so would be to select antibodies that bind tightly to the target antigen; this motivation flows directly from the prior art references themselves. Becker teaches that the treatment with antibodies is efficacious; Adair teaches that antibodies of IgG1 isotype bind to antigens very well, and Kuby teaches that the biological

properties of the specific isotypes is dependent upon the structure of the constant region, not the variable (antigen-binding) domain.

Applicant argues, on p. 13 of the remarks, that the references by Kuby and Adair fail to provide adequate guidance to selection of the IgG1 antibodies. Applicant argues that at p. 50, Adair teaches that the increased binding affinity of IgG1 antibodies to ICAM-1 is "unexpected because all these antibodies have identical binding sites". Applicant argues that this indicates the artisan of ordinary skill would not have been sufficiently guided to select the antibodies of the IgG1 isotype, as recited in the instant claims.

The examiner respectfully disagrees. First, it is noted that the references by Adair and Kuby point to the specific properties of IgG1 antibodies, and the artisan of ordinary skill would clearly understand that the advantages conferred by the IgG1 antibodies would be expected to be generalizable to all antiobides of this isotype, independent of the antigen to which they bind. See for example Adiar, p. 50 lines 4 – 13 teaches that the differences observed between the binding affinities of the various isotypes tested are attributed "to avidity alterations imposed on the antibodies by the differing hinge flexibility of the isotypes." Kuby (p. 123, second column, first complete paragraph) teaches that the four IgG isotypes differ in the hinge region and the number and position of inter-chain disulfide bonds. These are properties of the constant region, and therefore would not be expected to vary between antibodies that bind different antigens. As Adair attributed the differences in binding affinity between the various isotypes to physical differences in the hinge region, the skilled artisan would expect that the superior binding affinity of IgG1 antibodies would be expected to be common to all IgG1 antibodies, as they all share the same hinge.

Second, the examiner's determination that the difference between the prior art of record and the claimed invention would have been obvious to one of ordinary skill is consistent with the Supreme Court's recent decision in *KSR International Co. v. Teleflex Inc.* (82 USPQ2d 1385, 2007). The instant invention differs from Becker in that the instant invention recites the specific limitation of antibodies of the IgG1 isotype, whereas Becker is silent as to which particular isotype, if any, is to be used. However, Kuby teaches that IgG is the most abundant antibody in serum, and that there are only four IgG isotypes (known as IgG1 – IgG4). Of these, IgG1 is the most abundant. Selection of the most abundant isotype of the most abundant form of antibodies does not involve a particularly large inventive step, if any. Furthermore, in *KSR*, the Court ruled that "A person of ordinary skill in the art is also a person of ordinary creativity, not an

automaton." 82 USPQ2d at 1397. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Additionally, the Court ruled that an invention can be considered obvious when it is the result of choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. Here, given that there are only four known isotypes of IgG, selection of any one of the four would have been obvious; selection of the most abundant (IgG1) would have been particularly obvious.

On p. 13 of the remarks, applicant cites the references by Boel and by Preston in support of the argument that the artisan of ordinary skill would not have been motivated to select IgG1. The examiner respectfully disagrees. First, it is important to note that the reference by Boel was published a year after the instant application was filed and therefore cannot be properly relied upon for determinations of obviousness or teaching away from the claimed invention. Applicant cites p. 161 as being of particular relevance; the examiner is unable to find anything that teaches away from selection of IgG1. While Figure 4 (circled) and accompanying text indicates that all IgG isotypes perform equally, this does not constitute a teaching away from selection of IgG1, which Kuby identifies as the must abundant and which Adair teaches has increased antigen avidity owing to the structure of the constant region. The reference by Preston similarly does not teach away from the claimed invention, but rather indicates that chimeric antibodies have the same binding affinities as the parents from which they were derived.

12. Claims 1 - 2, 4, 10 - 12, 22-24, 31-32, 35-36, 82-84, 88-90, 95-99, 100-101, and 103-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Kuby and Adair as applied to claims 1 - 2, 4, 10 - 12, 22-24, 31-32, 36, 82-84, 88-90, 95-99, 101, and 103-104 above, and further in view of Miller (U.S. Patent 5,227,159 (of record)).

This rejection stands for the reasons of record. Applicant did not separately traverse the examiner's determination that the limitations recited in claim 35 would have been obvious to one of ordinary skill in the art given the teachings of Miller. Note the same limitation appears in claim 100.

13. Claims 1 - 2, 4, 10 - 12, 22-24, 31-32, 36-37, 82-84, 88-90, 95-99, and 101 -104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Kuby and Adair

as applied to claims 1 - 2, 4, 10 - 12, 22-24, 31-32, 36, 82-84, 88-90, 95-99, 101, and 103-104 above, and further in view of Sabel (U.S. Patent 4,883,666, of record).

This rejection stands for the reasons of record. Applicant did not separately traverse the examiner's determination that the limitations recited in claim 37 would have been obvious to one of ordinary skill in the art given the teachings of Sabel. Note the same limitation appears in claim 102.

14. Claims 1 - 2, 4, 6-8, 10 - 12, 22-24, 31-32, 36, 82-90, 95-99, 101, and 103-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Kuby and Adair as applied to claims 1 - 2, 4, 10 - 12, 22-24, 31-32, 36, 82-84, 88-90, 95-99, 101, and 103-104 above, and further in view of Brookmeyer (1998. American Journal of Public Health 88:1337-1342, of record.

This rejection stands for the reasons of record. Applicant did not separately traverse the examiner's determination that the limitations recited in claims 6-8 would have been obvious to one of ordinary skill in the art given the teachings of Brookmeyer. Note the same limitations appear in claims 85-87.

15. Claims 1 - 2, 4, 10 - 12, 17, 22-24, 31-32, 36, 82-84, 88-90, 93, 95-99, 101, and 103-104 rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Kuby and Adair as applied to claims 1 - 2, 4, 10 - 12, 22-24, 31-32, 36, 82-84, 88-90, 95-99, 101, and 103-104 above, and further in view of Yachi (EP 0 285 159, of record).

This rejection stands for the reasons of record. Applicant did not separately traverse the examiner's determination that the limitations recited in claim 17 would have been obvious to one of ordinary skill in the art given the teachings of Yachi. Note the same limitation appears in claim 93.

16. Claims 1 - 2, 4, 10 - 12, 21-24, 31-32, 36, 82-84, 88-90, 94-99, 101, and 103-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Kuby and Adair as applied to claims 1 - 2, 4, 10 - 12, 22-24, 31-32, 36, 82-84, 88-90, 95-99, 101, and 103-104 above, and further in view of Zhang et al. (1998. Current Protocols in Molecular Biology 10.15.1 - 10.15.9).

This rejection stands for the reasons of record. Applicant did not separately traverse the examiner's determination that the limitations recited in claim 21 would have been obvious to one of ordinary skill in the art given the teachings of Zhang. Note the same limitation appears in claim 94.

17. Claims 82 – 84, 87 – 90, 95 – 99, 101 – 102, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (US 5,589,154, of record) in view of Kuby (1997. Immunology, Third Edition, p. 123, cited in office action mailed 17 November 2006) and Adair et al. (WO 91/16928, cited in office action mailed 17 November 2006).

This rejection stands for the reasons of record. Applicant did not separately traverse the examiner's determination that the references by Anderson, Kuby, and Adair render obvious the recited claims.

18. Claims 82 – 84, 87 – 90, 95 – 99, 100 – 102, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson in view of Kuby and Adair as applied to claims 82 – 84, 87 – 90, 95 – 99, 101 – 102, and 104 above, and further in view of Miller (U.S. Patent 5,227,159, of record).

This rejection stands for the reasons previously made of record. Applicant did not separately traverse the examiner's determination that the limitations recited in claim 100 would have been obvious to one of ordinary skill in the art given the teachings of Miller.

19. Claims 82 – 84, 85 – 90, 95 – 99, 101 – 102, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson in view of Kuby and Adair as applied to claims 82 – 84, 87 – 90, 95 – 99, 101 – 102, and 104 above, and further in view of Brookmeyer (1998. American Journal of Public Health 88:1337-1342).

This rejection stands for the reasons previously made of record. Applicant did not separately traverse the examiner's determination that the limitations recited in claims 85-86 would have been obvious to one of ordinary skill in the art given the teachings of Brookmeyer.

20. Claims 82 – 84, 87 – 90, 93, 95 – 99, 101 – 102, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson in view of Kuby and Adair as applied to claims 82 – 84, 87 – 90, 95 – 99, 101 – 102, and 104 above, and further in view of Yachi (EP 0

285 159, published 10 May 1988).

This rejection stands for the reasons previously made of record. Applicant did not separately traverse the examiner's determination that the limitations recited in claim 93 would have been obvious to one of ordinary skill in the art given the teachings of Yachi.

21. Claims 82 – 84, 87 – 90, 95 – 99, 101 – 102, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson in view of Kuby and Adair as applied to claims 82 – 84, 87 – 90, 95 – 99, 101 – 102, and 104 above, and further in view of Zhang et al. (1998. Current Protocols in Molecular Biology 10.15.1 - 10.15.9).

This rejection stands for the reasons previously made of record. Applicant did not separately traverse the examiner's determination that the limitations recited in claim 94 would have been obvious to one of ordinary skill in the art given the teachings of Zhang.

New Rejections

Claim Rejections - 35 USC § 103

22. Claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker (EP 0 613 007, of record) in view of Walker (1994. Journal of Neuropathology and Experimental Neurology 53:377-383, cited on IDS filed 28 May 1999), Hanan (1996. Amyloid: Int. J. Exp. Clin Exp. Invest. 3:130-133, cited on IDS filed 28 May 1999), and Majocha et al. (U.S. Patent 5,231,000 issued 27 July 1993).

The examiner believes the rejections under 35 USC 103(a) above are proper. However, this additional rejection is being included as it points to antibody 10D5, an antibody of the IgG1 subclass which specifically binds Aβ.

Becker teaches administration of antibodies which bind to Aβ protein for treatment and diagnosis of Alzheimer's disease (see column 7 lines 44 – 52). Diagnosis is to be performed on patients not known to have the disease, and therefore is on point to prophylactic administration as recited in claim 82. Becker's antibodies include chimeric and humanized antibodies (see column 5 lines 50 – 58), which is on point to claims 1 and 11 – 12 an 89 - 90 as well as monoclonal antibodies, which are on point to claims 10 and 88. Note that the reference specifically teaches administration to humans for treatment and diagnosis of Alzheimer's (column 7), which is on point to claims 1 – 2, 4, 82 - 84. While claim 1 recites "a regime effective to ... treat the disease", no particular doses are recited within the claim and since the

prior art reference teaches treatment, it is presumed to be "effective". Similarly, claim 82 does not require any particular doses. Becker also teaches administration in pharmaceutical compositions further comprising carriers (see column 8 lines 19 – 42, which is on point to claims 24 and 97). The reference teaches that the antibodies are specific for Aβ protein in a β-sheet conformation (see column 5 lines 42 – 50), which is on point to claims 31 and 98 and further teaches that the protein only adopts this conformation after aging of the peptide in culture medium or water for at least 1 days (see paragraph spanning columns 2 – 3), therefore the antibodies which bind Aβ in β sheets would not be expected to bind full-length APP. Additionally Becker teaches administration routes including intravenous (see column 8), which is on point to claims 32 and 99. However Becker does not explicitly teach administration of antibodies of isotype IgG1 as recited in claims 1 and 82, does not explicitly teach administration of human monoclonal antibodies as encompassed by claims 10 and 88 and does not teach the specific doses recited in claims 22 – 23 and 95-96 or the duration of administration as recited in claim 36 and 101.

Walker teaches administration of mouse antibody 10D5 for imagining *in vivo* in primates. Walker teaches that the antibody is of isotype IgG1 (see p. 377 second column) and therefore is on point to claims 1 and 82. The reference teaches that the antibody recognizes Aβ in primate tissue *in situ* (bottom of p. 377, middle of first column on p. 379) and *in vivo* (p. 379). As explained above, *in vivo* administration for diagnostic imaging is on point to claim 82, drawn to administration to asymptomatic subjects. The reference indicates that administration of Aβ "has potential for delivering therapeutic agents that could prevent or reverse Ab deposition in the brains of patient with... Alzheimer's disease" (p. 382 end of first column), suggesting to the artisan of ordinary skill that the 10D5 IgG1 antibody is to be used for treating and delaying onset of disease. However Walker does not explicitly teach administration of humanized forms of 10D5 IgG1 antibody, as recited in claims 1 and 82.

Hanan teaches the effects of monoclonal antibody 10D5 on inhibiting the formation of Aβ aggregates in vitro. At p. 132 end of first column, Hanan teaches that 10D5 inhibits fibril formation by about 80-90%; see also Figure 1 on the same page. Compared to the other antibodies tested, 10D5 and 6C6 were about equal to one another and were superior to other antibodies tested; see Figure 1. Hanan suggests to the artisan of ordinary skill that antibodies or fragments thereof could be used as therapeutics for Alzheimer's disease, which is on point to

claims 1-2. However Hanan does not explicitly teach administration to patients *in vivo*, and does not teach humanized antibodies as recited in claims 1 and 82.

Claims 103 – 104 recite certain properties of the antibody. The examiner is unable to determine if the antibodies rendered obvious by Becker in view of Walker and Hanan have this property. However, inclusion of these claims in this rejection is proper as the claims recite no additional structural limitations beyond those of the parent claims. As the references render obvious administration of the antibodies of isotype IgG1 for the reasons of record and further explained below, claims 103-104 are properly included even though the prior art references are silent as to a property which appears to be inherent; see MPEP § 2112.

It would have been obvious to one of ordinary skill in the art to use monoclonal antibody 10D5, which is of isotype IgG1 as taught by Walker, in the methods of administering antibodies taught by Becker. Furthermore it would have been obvious to one of ordinary skill in the art to humanize the antibody, as taught by Becker. The motivation to do so comes from the prior art references themselves. Becker teaches administration of antibodies for treatment of Alzheimer's and administration to patients not known to have the disease. Becker also teaches that humanizing antibodies is advantageous at minimizes the degree of immune response elicited by removing most of the foreign epitopes, and teaches that it is within the skill of the ordinary artisan to humanize an antibody. Walker teaches that 10D5 antibody is of isotype IgG1, and teaches that the antibody specifically binds to Aβ both in vitro and in vivo. Hanan further guides selection of 10D5 based on its superior ability to inhibit aggregation. Additionally administration for at least 6 months as recited in claims 36 and 101 would have been obvious, in order to ensure complete treatment.

The examiner is aware that a similar rejection under 35 USC 103(a) has previously been made of record and was discussed by applicant in the Appeal Brief filed 27 June 2006. In the Brief, applicant's representative argued against the examiner's determination of obviousness. Arguments included:

1) The ways each reference teach the specific limitations of the claims has not been made sufficiently clear,

2) The reference by Paul p. 838, filed by applicant 24 August 2005 indicates that mouse IgG1 is most structurally similar to human IgG2 and therefore teaches away from the claimed invention, and

3) There was no reasonable expectation of success.

The arguments have been fully considered but they are not persuasive. With respect to 1), the examiner believes that the way each of the references by Becker, Walker, and Hanan address each of the claim limitations is thoroughly explained above. With respect to 2), the examiner is unable to find specific teachings in the Paul reference indicating that mouse IgG1 is the structural equivalent of anything other than IgG1 in humans. While the reference discusses the relative affinity of various isotypes in different for Fc receptors, the reference does not teach that the structural properties of human IgG1 are most like those of mouse IgG2, as argued by applicant at p. 7 of the Brief filed 27 June 2006. With respect to 3), Majocha et al. (U.S. Patent 5,231,000 issued 27 July 1993) teach that antibodies against Aβ protein are suitable for *in vivo* diagnosis of Alzheimer's disease (note Majocha uses the term "A4" which is synonymous with Aβ; see Becker column 1 second paragraph). Majocha specifically teaches that the antibodies against Aβ protein can be used for *in vivo* diagnostic imaging (column 5 lines 15 – 55, for example; see also claims 7 – 9 which encompass *in vivo* detection of Aβ protein in brain tissue with the antibodies). As Majocha, issued well over a year before the effective filing date of the instant application, teaches and claims such *in vivo* detection by administering the antibodies, the artisan of ordinary skill immediately understand that the antibodies are able to cross the blood brain barrier. Thus the artisan would have a reasonable expectation of succeeding in the methods now claimed, which similarly require administration of antibodies that bind Aβ and which might also require the antibodies to cross the BBB (note that only claims 32 and 99 recite specific routes of administration; all other claims subject to this rejection are sufficiently broad to encompass intracisternal administration taught by Walker).

23. Claims 1-2,4, 10 – 12, 24, 31-32, 35-36, 82-84, 88-90 97-101, and 103-104 rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Walker, Hanan, and Majocha as applied to claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 above, and further in view of Miller (U.S. Patent 5,227,159, of record).

The reasons why claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 are rendered obvious by Becker, Walker, Hanan, and Majocha are set forth above. However none of these references teaches monitoring the patient for antibody levels as recited in claims 35 and 100.

Miller teaches administration of anti-HIV antibodies for treatment of disease. Miller also teaches measuring the levels of antibodies and repeating administration of the antibody as

indicated by the circulating antibody levels (see column 15 lines 52 - 62), which is on point to claim 35. However Miller does not teach treatment of Alzheimer's disease by administration of antibodies which bind Aβ.

It would have been obvious to monitor antibody levels as taught by Miller, when treating Alzheimer's disease by administering antibodies that bind to Aβ protein as taught by Becker. The motivation to do so would be to optimize the circulating level of antibody, thereby ensuring that a therapeutic dose was maintained.

24. Claims 1-2,4, 10 – 12, 24, 31-32, 36-37, 82-84, 88-90 97-99, and 101-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Walker, Hanan, and Majocha as applied to claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 above, and further in view of Sabel (U.S. Patent 4,883,666, of record).

The reasons why claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 are rendered obvious by Becker, Walker, Hanan, and Majocha are set forth above. However none of these references teaches sustained release compositions as recited in claims 37 and 102.

Sabel teaches implantation of controlled release systems for treatment of neurological diseases (see column 10 - column 12). Sabel teaches the implants are suitable for administration to patients with Alzheimer's disease (column 5 lines 5 - 26). However Sabel does not teach administration of antibodies which bind to Aβ for treatment of the disease.

It would have been obvious to one of ordinary skill in the art to implant a controlled release system to administer the antibodies, as taught by Sabel, with a reasonable expectation of success. Sabel teaches there are many advantages to implantation of controlled release systems, including constant predictable release and local administration, thereby obviating the need for high systemic doses (see column 2 lines 49 - 65).

25. Claims 1-2,4, 6-8,10 – 12, 24, 31-32, 36, 82-87, 88-90 97-99, 101, and 103-104 rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Walker, Hanan, and Majocha as applied to claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 above, and further in view of Brookmeyer (1998. American Journal of Public Health 88:1337-1342, of record).

The reasons why claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 are rendered obvious by Becker, Walker, Hanan, and Majocha are set forth above. However none of these references teaches administering to patients under 50, as recited in claims 6 and 85, or patients with either inherited (claims 7 and 86) or no known (claims 8 and 87) risk factors.

Brookmeyer teaches that the incidence of Alzheimer's disease increases as people age, and further teaches that delaying onset or reducing severity even slightly would result in enormous savings, given the expected financial burden of the disease and the increasing percentage of the population that will live to old age. However Brookmeyer does not teach administration of antibodies which bind to Aβ for treatment of the disease.

It would have been obvious to one of ordinary skill in the art to use the method of Becker to treat patients under 50, or patients either with or without known risk factors, with a reasonable expectation of success. The motivation to do so would be to delay the onset of the disease, which would result in considerable savings.

26. Claims 1-2,4, 10 – 12, 17, 24, 31-32, 36, 82-84, 88-90,93, 97-99, 101, and 103-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Walker, Hanan, and Majocha as applied to claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 above, and further in view of Yachi (EP 0 285 159, of record).

The reasons why claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 are rendered obvious by Becker, Walker, Hanan, and Majocha are set forth above. However none of these references teaches administering a second antibody that binds to amyloid deposit as recited in claims 17 and 93.

Yachi teaches a second antibody that binds to Aβ protein. However Yachi does not teach administration for treatment of disease.

It would have been obvious to one of ordinary skill in the art to co-administer the antibodies from Becker and Yachi, with a reasonable expectation of success. It is *prima facie* obvious to co-administer two compounds known to be suitable for the same purpose (MPEP § 2144). Becker and Yachi teach antibodies that bind Aβ, and Becker teaches they are suitable for treatment of Alzheimer's.

27. Claims 1-2,4, 10 – 12, 21, 24, 31-32, 36, 82-84, 88-90, 94, 97-99, 101, and 103-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker in view of Walker, Hanan, and Majocha as applied to claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 above, and further in view of Zhang et al. (1998. Current Protocols in Molecular Biology 10.15.1 - 10.15.9).

The reasons why claims 1-2,4, 10 – 12, 24, 31-32, 36, 82-84, 88-90 97-99, 101, and 103-104 are rendered obvious by Becker, Walker, Hanan, and Majocha are set forth above. However none of these references teaches heterologous peptides fused to the antibodies as recited in claims 21 and 94.

Zhang et al. teach labeling by epitope-tagging for detection of molecules. It would have been obvious to one of ordinary skill in the art to epitope tag the antibody of Becker, as taught by Zhang et al., with a reasonable expectation of success. A motivation to do so would be to detect the antibody in a heterogeneous sample. Becker teaches that their antibodies are useful for detection in diagnostic assays (see column 7). Because these are heterogenous samples using a labeled antibody as taught by Zhang is particularly useful, as the epitope allows for easy detection.

Double Patenting

28. Claims 1 – 2, 4, 6 – 8, 10 - 12, 17, 21 – 24, 31 – 32, 35 – 37, 82 – 90, and 93 – 104 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18 – 22 of copending Application No. 11/520438. Although the conflicting claims are not identical, they are not patentably distinct from each other because in the '438 case the claims are drawn to the specific humanized IgG1 antibody 10D5 whereas in the instant case the claims are generic to all humanized IgG1 antibodies that bind Aβ.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

29. No claim is allowed.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Daniel E. Kolker
Patent Examiner

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